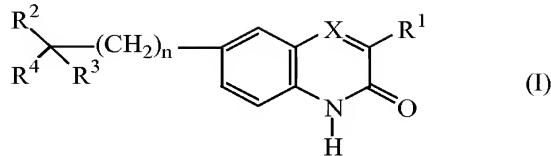


CLAIMS

1. A compound of formula (I),



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1 or 2;

$\text{X}$  is N or  $\text{CR}^5$ , wherein  $\text{R}^5$  is hydrogen or taken together with  $\text{R}^1$  may form a bivalent radical of formula  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ ;

15  $\text{R}^1$  is  $\text{C}_{1-6}\text{alkyl}$  or thienyl;

$\text{R}^2$  is hydrogen or hydroxy or taken together with  $\text{R}^3$  or  $\text{R}^4$  may form  $=\text{O}$ ;

$\text{R}^3$  is a radical selected from

20  $-(\text{CH}_2)_s-\text{NR}^6\text{R}^7$  (a-1),  
-O-H (a-2),  
-O- $\text{R}^8$  (a-3),  
-S-  $\text{R}^9$  (a-4), or  
—C≡N (a-5),

25 wherein

s is 0, 1, 2 or 3;

$\text{R}^6$  is  $-\text{CHO}$ ,  $\text{C}_{1-6}\text{alkyl}$ , hydroxy $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}\text{alkylcarbonyl}$ ,

di( $\text{C}_{1-6}\text{alkyl}$ )amino $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}\text{alkylcarbonylaminoC}_{1-6}\text{alkyl}$ , piperidinyl $\text{C}_{1-6}\text{alkylaminocarbonyl}$ , piperidinyl, piperidinyl $\text{C}_{1-6}\text{alkyl}$ ,

30 piperidinyl $\text{C}_{1-6}\text{alkylaminocarbonyl}$ ,  $\text{C}_{1-6}\text{alkyloxy}$ , thienyl $\text{C}_{1-6}\text{alkyl}$ , pyrrolyl $\text{C}_{1-6}\text{alkyl}$ , aryl $\text{C}_{1-6}\text{alkylpiperidinyl}$ , arylcarbonyl $\text{C}_{1-6}\text{alkyl}$ , arylcarbonylpiperidinyl $\text{C}_{1-6}\text{alkyl}$ , haloindozolylpiperidinyl $\text{C}_{1-6}\text{alkyl}$ , or aryl $\text{C}_{1-6}\text{alkyl}(\text{C}_{1-6}\text{alkyl})\text{aminoC}_{1-6}\text{alkyl}$ ;

$\text{R}^7$  is hydrogen or  $\text{C}_{1-6}\text{alkyl}$ ;

35  $\text{R}^8$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}\text{alkylcarbonyl}$  or di( $\text{C}_{1-6}\text{alkyl}$ )amino $\text{C}_{1-6}\text{alkyl}$ ; and

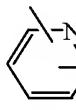
R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
or R<sup>3</sup> is a group of formula

-Z-

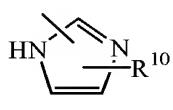
(b-1),

wherein

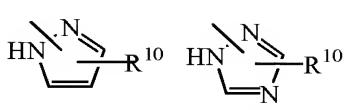
5 Z is a heterocyclic ring system selected from



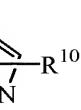
(c-1)



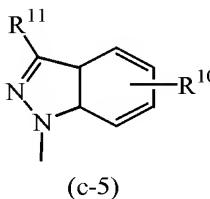
(c-2)



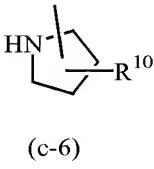
(c-3)



(c-4)



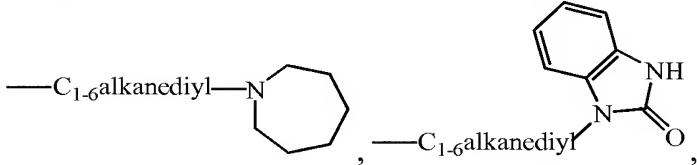
(c-5)



(c-6)

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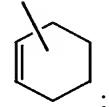
wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,



C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl,

di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl,

15 aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino, C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;



R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or

20 aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy;

with the proviso that when

n is 0, X is N, R<sup>2</sup> is hydrogen, R<sup>3</sup> is a group of formula (b-1), Z is the heterocyclic ring system (c-2) or (c-4) wherein said heterocyclic ring system Z is attached to the rest of the molecule with a nitrogen atom, and R<sup>10</sup> is hydrogen; then

25 R<sup>4</sup> is other than C<sub>1-6</sub>alkyl or pyridinyl.

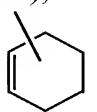
2. A compound as claimed in claim 1 wherein

n is 0 or 1; X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen; R<sup>3</sup> is a radical selected from (a-1), (a-2) or (a-3) or is a group of formula (b-1) i.e. -Z-; s is 0, 1 or 2; R<sup>6</sup> is -CHO, C<sub>1</sub>-alkyl, piperidinylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl or

5 arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; R<sup>8</sup> is C<sub>1-6</sub>alkyl; when R<sup>3</sup> is a group of formula (b-1) then Z is a heterocyclic ring system selected from (c-2) or (c-4); and each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino.

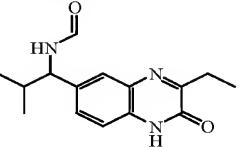
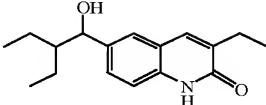
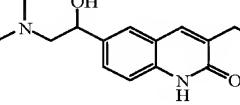
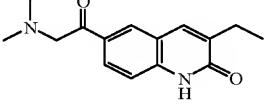
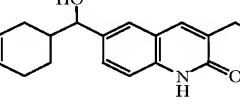
3. A compound according to claim 1 and 2 wherein

10 n is 0; X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen; R<sup>1</sup> is C<sub>1-6</sub>alkyl; R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>4</sup> may form =O; R<sup>3</sup> is a radical selected from (a-1) or (a-2); s is 0 or 1; R<sup>6</sup> is -CHO or C<sub>1-6</sub>alkyl; and R<sup>4</sup> is



hydrogen, C<sub>1-6</sub>alkyl or .

15 4. A compound according to claim 1, 2 and 3 wherein the compound is selected from compound No 1, compound No 5, compound No 7, compound No 3 and compound No 17.

	compound 1		compound 5
	compound 7		compound 3
	compound 17		

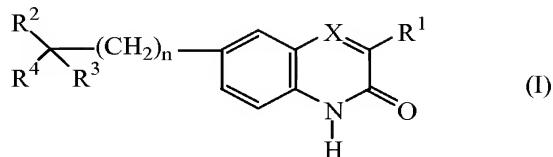
5. A compound as claimed in any of claims 1 to 4 for use as a medicine.

20

6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 4.

25 7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 4 are intimately mixed.

8. Use of a compound for the manufacture of a medicament for the treatment of a PARP mediated disorder, wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1 or 2;

X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

15 R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

20 -(CH<sub>2</sub>)<sub>s</sub>- NR<sup>6</sup>R<sup>7</sup> (a-1),  
-O-H (a-2),  
-O-R<sup>8</sup> (a-3),  
-S- R<sup>9</sup> (a-4), or  
—C≡N (a-5),

25 wherein

s is 0, 1, 2 or 3;

R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl,

di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, piperidinyl, piperidinylC<sub>1-6</sub>alkyl,

30 piperidinylC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl, pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidinyl, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl, haloindozolylpiperidinylC<sub>1-6</sub>alkyl, or arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;

35 R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and

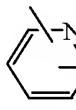
R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
or R<sup>3</sup> is a group of formula

-Z-

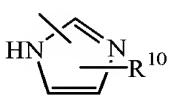
(b-1),

wherein

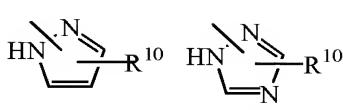
5 Z is a heterocyclic ring system selected from



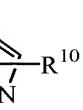
(c-1)



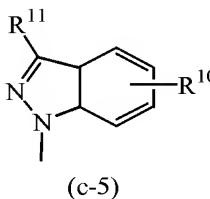
(c-2)



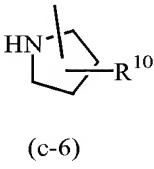
(c-3)



(c-4)



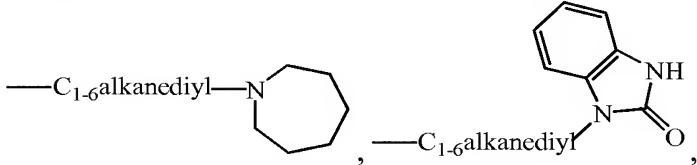
(c-5)



(c-6)

10

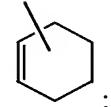
wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,



C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl,

di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl,

15 aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino, C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;



R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or

aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy.

20

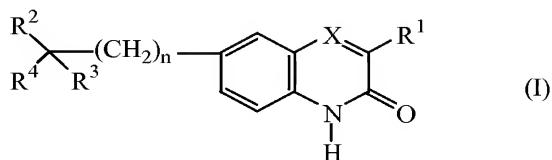
9. Use according to claim 8 of a PARP inhibitor of formula (I) for the manufacture of a medicament for the treatment of a PARP-1 mediated disorder

10. Use according to claim 8 and 9 wherein the treatment involves chemosensitization.

25

11. Use according to claim 8 and 9 wherein the treatment involves radiosensitization.

12. A combination of a compound with a chemotherapeutic agent wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

10

X is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

15

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

-(CH<sub>2</sub>)<sub>s</sub>-NR<sup>6</sup>R<sup>7</sup> (a-1),

20 -O-H (a-2),

-O-R<sup>8</sup> (a-3),

-S- R<sup>9</sup> (a-4), or

—C≡N (a-5),

wherein

25 s is 0, 1, 2 or 3;

R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, piperidinyl, piperidinylC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl,

30 pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidinyl, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl, haloindozolylpiperidinylC<sub>1-6</sub>alkyl, or arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;

R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and

35 R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;

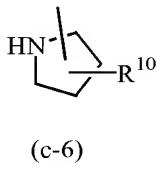
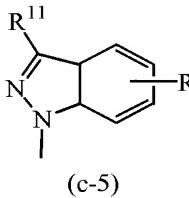
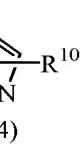
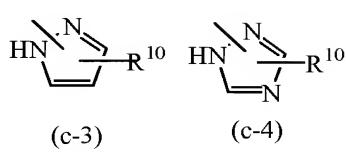
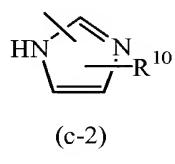
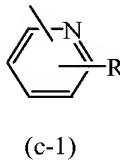
or R<sup>3</sup> is a group of formula

-Z- (b-1),

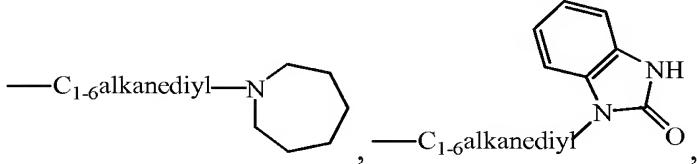
wherein

Z is a heterocyclic ring system selected from

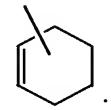
5



10 wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,



C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl, di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl, aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino, C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;

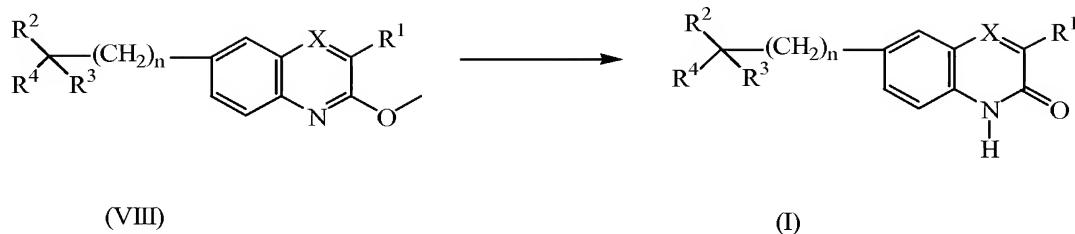


R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or ;

aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy.

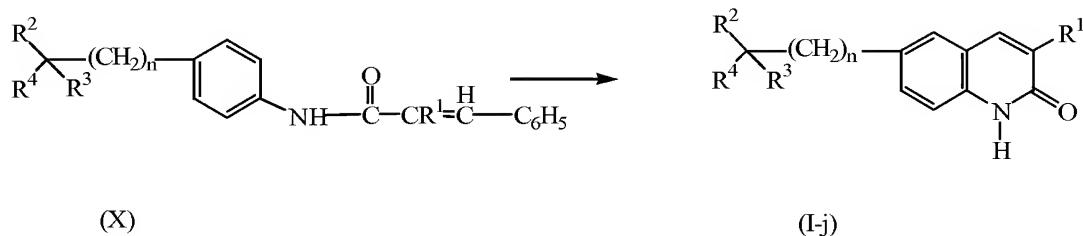
20 13. A process for preparing a compound as claimed in claim 1, characterized by

a) the hydrolysis of intermediates of formula (VIII), according to art-known methods, by submitting the intermediates of formula (VIII) to appropriate reagents, such as, tinchloride, acetic acid and hydrochloric acid, in the presence of a reaction inert solvent, e.g. tetrahydrofuran.



b) the cyclization of intermediates of formula (X), according to art-known cyclizing procedures into compounds of formula (I) wherein X is CH herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents.

10



15

c) the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) wherein  $\text{R}^{\text{h}}$  is  $\text{C}_{1-6}\text{alkyl}$ , into compounds of formula (I), wherein X is N, herein referred to as compounds of formula (I-i), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like.

